UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/309,689	05/11/1999	NORMAN ORENTREICH	4555-45	7858

570 7590 06/02/2004

AKIN GUMP STRAUSS HAUER & FELD L.L.P.
ONE COMMERCE SQUARE
2005 MARKET STREET, SUITE 2200
PHILADELPHIA, PA 19103-7013

EXAMINER	
MOHAMED, ABDEL A	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/309,689	ORENTREICH ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

ACKNOWLEFMENT FOR RECONSIDERATION AFTER FINAL, STATUS OF THE APPLICATION AND CLAIMS

1. The request for reconsideration After Final filed 4/21/04 is acknowledged, entered and considered. Claims 23-42 are now pending in the application. The rejection under 35 U.S.C. 103(a) over the prior art of record is withdrawn in view of Applicant's arguments filed 4/21/04. The Finality of the previous Office action is withdrawn in view of granting Applicant's petition to withdraw finality of the first Office action mailed 9/17/03 and in view of the following new ground of rejection.

CLAIM REJECTIONS-35 U.S.C. § 103(a)

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 23-26, 29-32 and 34-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coleman III, et al. ([Eds.] Skin resurfacing, pp. 217-234, 1998) in view of Grabarek et al. (Analytical Biochemistry, Vol. 185, pp. 131-135, 1990) and Wong (Chemistry of Protein Conjugation and Cross-linking, pp. 39-40 and 195-207, 1991).

Claims 23-26, 29-32 and 34-42 are directed to an injectable material for soft tissue augmentation comprising cross-linked blood plasma proteins, wherein the cross-linkages comprise at least one intermolecular amide bond such as lysine-glutamate bond or lysine-asparate bond which are cross-linked with a zero-length-cross-linking agent and that the cross-linked proteins are purified and/or sterilized and the blood protein can be obtained from an autologous blood sample, and to a method of preparing an injectable material as well as injecting the material thereof into an intradermal compartment of the skin of the mammal.

The reference of Coleman III, et al., teaches the use of FIBREL containing porcine gelatin powder mixed with patients own plasma and ϵ-amino caproic acid applicable as sterile kit, wherein the FIBREL is an injectable material for soft tissue augmentation of wrinkles comprising cross-linked, blood plasma proteins that are purified and sterilized. The references show the administration of the injectable material in combination with an anesthetic compound such as lidocaine into an intradermal compartment of the skin of a patient (See e.g., page 222 under the heading FIBREL) as

directed to claims 23, 29 and 39-41. Thus, the reference shows the administration of the injectable material in combination with an anesthetic compound such as lidocane into an intradermal compartment of the skin of the patient as well as method of preparing such formulations thereof.

Coleman III, et al. differ from claims 23-26, 29-32 and 34-42 in not teaching the use of a cross-linked blood plasma proteins wherein the cross-linkages comprise at least one intermolecular amide bond which comprise zero-length cross-linked, blood plasma proteins, wherein the zero-length cross-linked blood plasma proteins contain an amide bond cross-link such as lysine-glutamate bond or lysine-aspartate bond and the ratio of cross-linked, plasma proteins is from 1% to about 10% by weight of injectable material. The primary reference shows mixing the patient's own plasma with gelatin powder and ϵ-amino caproic acid. This is a clear indication that cross-linkage of blood plasma protein has occurred in the reconstitution step from the FIBREL to be useful for filling depressed defects in a patient. However, use of cross-linking agents are known in the art, particularly, such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) for the purpose of crosslinking protein-protein complexes as taught by the secondary reference of Garbarek et al. The reference teaches on page 131 that the zero-length crosslinking procedure with the use of active esters such as EDC for inducing isopeptide bonds between amino acid side-chains in proteins in aqueous solution. The reference also states that the crosslinking agent should be used at a 5-to 10-fold dilution than the complexed protein and as such overlaps with the amounts disclosed in claims 26 and 38 using the agent (EDC) of claims 36 and 37. Further, on page 134, bridging

page 135, the reference clearly shows that zero-length crosslinking with carbodiimides intramolecular crosslinking can occur if there are $NH+_3$ - COO- interaction with the protein. Such interactions are known to be involved in stabilization of the 3D structure of proteins as, for example, in the "I to I +4" type interactions between Lys and Glu (or Asp) side chains in α-helical segments. Thus, clearly showing that the amide bond cross-link comprises a lysine-glutamate amide bond or a lysine-aspartate amide bond, and as such meets the limitation of claim 25. Furthermore, the secondary reference of Wong discloses the various zero-length cross-linking reagents under A to E for the purpose of inducing the direct joining of, and create stable bonds between, two intrinsic chemical moieties of one or more polypeptide chains, without the introduction of any extrinsic matter (See e.g. pages 195-202). Thus, the reference meets the limitations of claim 36.

Therefore, given the teachings of the primary reference, one of ordinary skill in the art would have been motivated to adapt the above scheme of using of a cross-linked blood plasma proteins which comprise zero-length cross-linked, blood plasma proteins, wherein the zero-length cross-linked blood plasma proteins contain an amide bond cross-link such as lysine-glutamate bond or lysine-aspartate bond. Furthermore, such features are known or suggested in the art, as seen in the secondary references, and including such features into the injectable material for soft tissue augmentation in mammals comprising cross-linked, blood plasma proteins of the primary references of Coleman III, et al. would have been obvious to one of ordinary skill in the art to obtain the known and recognized functions and advantages thereof of using a tissue

augmentation device that comprises blood proteins which are cross-linked, wherein the cross-linkages include at least one amide bonds. Thus, in view of the above, and in view of the combined teachings of the prior art; one of ordinary skill in the art would have been motivated at the time the invention was made to use the already known injectable material for soft tissue augmentation comprising cross-linked, blood plasma proteins which are cross-linked, wherein the cross-linkages comprise at least one intermolecular amide bond with a zero-length-cross-linking agent such as EDC as discussed in the secondary references for the intended purpose of obtaining or producing a safe, non-antigenic, non-irritating, longer-lasting and aesthetically-pleasing injectable materials for soft tissue augmentation which are relatively easy to obtain and/or manufacture.

Accordingly, claims 23-26, 29-32 and 34-42 are prima facie obvious over the prior art, because it would be within the ordinary skill of the art to easily adapt the already known system of zero-length crosslinking procedure described in the prior art of the secondary references which is applicable to all kinds of proteins including blood plasma proteins for the intended purpose of cross-linking blood plasma proteins to form materials which are injectable and could be used in a method of augmenting a soft tissue defect in a skin area of a mammal by injecting the material into an intradermal compartment of the skin of the mammal is an obvious modification of the prior art combined teachings at the time the invention was made, absent of sufficient objective factual evidence or unexpected results to the contrary.

3. Claims 27, 28 and 33 rejected under 35 U.S.C. 103(a) as being unpatentable over Coleman III, et al. ([Eds.] Skin resurfacing, pp. 217-234, 1998) in view of Grabarek et al. (Analytical Biochemistry, Vol. 185, pp. 131-135, 1990) and Wong (Chemistry of Protein Conjugation and Cross-linking, pp. 39-40 and 195-207, 1991) as applied to claims 23-26, 29-32 and 34-42 above, and further in view of Wang et al. (Journal of the Parenteral Drug Association, Vol. 34, No. 6, pp. 452-462, November-December 1980).

The reference of Wang et al. reviews the various excipient (additives) and pH's for parenteral products in which the reference focuses on products with extreme pHs, and shows the tabulation of pH range, acid or base used for adjustment, and product identity. The reference also discloses numerous physiological acceptable fluids as additives for parenteral formulations, which includes anesthetic compounds such as procaine among others for local administration. Thus, the reference clearly teaches the use of a physiologically acceptable fluid and the acidification of the fluid thereof (See e.g., the entire document and particularly pages 452 and 460) as directed to claims 27, 28 and 33.

Therefore, in view of the above, and in view of the combined teachings of the prior art; one of ordinary skill in the art would have been motivated at the time the invention was made to use the already known injectable material for soft tissue augmentation comprising cross-linked, blood plasma proteins which are cross-linked, wherein the cross-linkages comprise at least one intermolecular amide bond crosslink such as lysine-glutamate bond or lysine-asparate bond and the ratio of the cross-linked, plasma protein is from 1% to about 10% by weight of injectable material to the

physiologically acceptable fluid of from 99% to about 90% by weight of the injectable material with a zero-length-cross-linking agent such as EDC as discussed in the secondary references for the intended purpose of obtaining or producing a safe, non-antigenic, non-irritating, longer-lasting and aesthetically-pleasing injectable materials for soft tissue augmentation which are relatively easy to obtain and/or manufacture.

Accordingly, claims 23-42 are prima facie obvious over the prior art, because it would be within the ordinary skill of the art in view of the combined teachings of the prior art to employ an injectable material for soft tissue augmentation, methods of preparing an injectable material for soft tissue augmentation, and methods of soft tissue augmentation in which the injectable material is used to aesthetically correct scars, wrinkles, and other similarly depressed dermal defects by filling the depression that creates the defect, absent of sufficient objective factual evidence or unexpected results to the contrary.

ARGUMENTS ARE NOT PERSUASIVE

4. Applicant's declaration filed 7/11/03 and arguments filed 4/21/04 have been fully considered but they are not persuasive. Applicant's arguments that none of the cited references either alone or in combination teaches, discusses, or suggests use of the disclosed processes or reagents to produce an injectable material for tissue augmentation comprising cross-linked blood plasma proteins, wherein the cross-linkages comprise at least one intermolecular amide bond. Further, Applicant argues by stating that the Examiner has made no showing nor has he provided an explanation as to where the disclosure of cross-linked plasma protein occurs in Coleman. Thus, there

is no teaching or suggestion in the primary reference that any proteins that may be present in the blood plasma used to reconstitute the FIBRIL composition are cross-linked in any manner is not persuasive. Contrary to Applicant's arguments and the declaration filed 7/11/03, the primary references of Coleman III, et al. as discussed above clearly discloses like the instantly claimed invention an injectable material for soft tissue augmentation of wrinkles comprising cross-linked, blood plasma proteins that are purified and sterilized. On page 222, left column, paragraph 2, the primary reference discusses **mixing** the patient's own plasma with gelatin powder and ϵ-amino caproic acid. Although, as argued by Applicant and supported by the declaration that FIBRIL composition itself does not constitute any blood plasma proteins and a collagen is not a blood plasma protein, however, by mixing the patient's own plasma, one of ordinary skill in the art would assume by virtue of "mixing" alone that it is natural or inherent or expected when you mix blood plasma with collagen or any protein of interest that crosslinkage occurs. Further, the reference has shown that cross-linkage of blood plasma protein has occurred in the reconstitution step from the FIBREL to be useful for filling depressed defects in a patient. For further support see Applicant's Declaration at ¶ 27 and Applicant's remarks filed 4/21/04 on page 6, last paragraph which states that Coleman discloses that the formation of cross-linkages between and among blood plasma proteins is undesirable. Thus, in view of this and in view for the reasons discussed above, there is teaching or suggestion in the primary reference that collagen (any protein may be present) in the blood plasma used to reconstitute the FIBREL composition are cross-linked.

Further, the references show the administration of the injectable material in combination with an anesthetic compound such as lidocaine into an intradermal compartment of the skin of a patient. Thus, the primary references clearly teach the use

of injectable material for tissue augmentation comprising cross-linked blood plasma proteins. Furthermore, as admittedly acknowledged by Applicant and as taught by the primary references that the use and the composition of the FIBRIL tissue augmentation device reconstituted with a patients blood plasma in view of independent claims 23, 30 and 31 claims language "comprising" which would not exclude other types of blood plasma proteins, and cross-link them taken with the teachings of the secondary references to arrive at the present claimed invention for the reasons stated above.

Applicant assertion that even if the Examiner's suggested combination did teach or suggest each and every element of the claimed invention, which they do not, such combination do not render the claimed invention obvious, for there was no motivation or suggestion in the art to combine references as suggested by the Examiner to arrive at the present invention is noted. However, Applicant's assertion is unpersuasive because given the teachings of the primary reference, one of ordinary skill in the art would have been motivated to use cross-linking agents which are known in the art and taught by the secondary references as discussed above and adapt the above scheme of using of a cross-linked blood plasma proteins which comprise zero-length cross-linked, blood plasma proteins, wherein the zero-length cross-linked blood plasma proteins contain an amide bond cross-link such as lysine-glutamate bond or lysine-aspartate bond. Furthermore, such features are known or suggested in the art, as seen in the secondary references, and including such features into the injectable material for soft tissue augmentation in mammals comprising cross-linked, blood plasma proteins of the primary reference of Coleman III, et al. would have been obvious to one of ordinary skill in the art to obtain the known and recognized functions and advantages thereof of using a tissue augmentation device that comprises blood proteins which are cross-linked, wherein the cross-linkages include at least one amide bonds. Thus, in view of the

above, and in view of the combined teachings of the prior art; one of ordinary skill in the art would have been motivated at the time the invention was made to use the already known injectable material for soft tissue augmentation comprising cross-linked, blood plasma proteins which are cross-linked with a zero-length-cross-linking agent such as EDC as discussed in the secondary references for the intended purpose of obtaining or producing a safe, non-antigenic, non-irritating, longer-lasting and aesthetically-pleasing injectable materials for soft tissue augmentation which are relatively easy to obtain and/or manufacture.

The declaration and Applicant's response assert that blood plasma proteins, which are normally soluble and biodegradable and do not serve any cell signaling or recruiting function, are not capable of recruiting fibroblasts to enable the secretion of collagen, and the subsequent "filling" of the intradermal skin compartment into which the composition is injected as taught by the combined teachings of the prior art. Applicant's response and the declaration seem to imply that such modification in the claimed invention would not result in a tissue augmentation device that comprises blood proteins which are cross-linked, wherein the cross-linkages include at least one amide bond. However, there is no indication of this in the claims as written.

Thus, the combined teachings of the prior art clearly teach the use of an injectable material for soft tissue augmentation comprising cross-linked blood plasma proteins, wherein the cross-linkages comprise at least one intermolecular amide bond such as lysine-glutamate bond or lysine-asparate bond which are cross-linked with a zero-length-cross-linking agent and that the cross-linked proteins are purified and/or sterilized and the blood protein can be obtained from an autologous blood sample, and to a method of preparing an injectable material thereof as well as injecting the material into an intradermal compartment of the skin of the mammal.

In regard to Applicant's allegation that unexpected result achieved by the invention because the tissue augmentation composition of the invention, once injected, last longer than the prior art compositions that use collagen as does FIBREL, for the inventive composition it is less rapidly degraded by the proteases and immune system components present in the human patient, and the tissue augmentation composition of the invention was found to have an average rating of 3.019 by day 693 is noted. However, for Applicant to show unexpected results as alleged, Applicant has to provide side by side comparison with unexpected results showing that there is patentable difference between the invention's method and the closest prior art method of making and using an injectable material for soft tissue augmentation.

CONCLUSION AND FUTURE CORRESPONDENCE

5. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272-0955. The examiner can normally be reached on Monday through Friday from 5:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (571) 272-0951. The appropriate fax phone number for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 305-7401 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Mohamed/AAM

May 28, 2004